

Full Text AR-94-005

BASIC OSTEOPOROSIS NEW EXPERIMENTAL STRATEGIES

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P.T.

Keywords:

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute on Aging

Letter of Intent Receipt Date: June 28, 1994

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PURPOSE

The Bone Biology and Bone Diseases Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the Bone and Mineral Research Program of the Endocrinology Research Section of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Geriatrics and Biology of Aging Programs of the National Institute on Aging (NIA) invite investigator-initiated research project grant applications to encourage and facilitate research projects designed to develop promising basic cellular, molecular, physiological, and genetic approaches to osteoporosis.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This Request for Applications (RFA), Basic Osteoporosis New Experimental Strategies, is

related to the priority areas of diabetes and chronic disabling conditions and older adults and preventive services. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Applications may be submitted by single institutions and by a consortia of institutions. Foreign institutions are not eligible for First Independent Research and Support and Transition (FIRST) (R29) awards. Applications from minority individuals and women are encouraged.

MECHANISM OF SUPPORT

Support for this program will be through investigator-initiated research grant applications (R01) and FIRST (R29) awards.

This RFA is a one-time solicitation for fiscal year 1995. However, the NIAMS, NIDDK, and NIA may reissue the RFA in future years. If there is a continuing program need, the NIAMS, NIDDK, and NIA will invite recipients of awards under this RFA to submit competitive continuation applications.

Responsibility for planning and implementation of the proposed project will be solely that of the applicant. The total project period for R01 applications submitted in response to the present RFA may not exceed four years. FIRST awards must be for five years. The anticipated award date is April 1, 1995.

FUNDS AVAILABLE

Approximately \$2,000,000 in total costs per year for four years will be committed by the NIAMS to fund applications submitted in response to this RFA. An additional \$500,000 will be committed by the NIDDK, and an additional \$600,000 by the NIA. This funding level is dependent on the receipt of a sufficient number of applications of high scientific merit. The direct cost of each R01 project is limited to \$160,000 for the first year and R29s are limited to \$70,000. Thus it is

anticipated that a total of 12 to 14 projects will be funded in FY 95. Although this program is provided for in the financial plans of the NIAMS, NIDDK, and NIA, the award of grants, as well as the final amounts awarded, will be contingent upon the availability of funds for this purpose.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or principal investigator should be included with the application.

RESEARCH OBJECTIVES

Background

Much work remains to be done in order to counter the disabling, costly consequences of osteoporosis. Means of targeting nutritional and pharmacological preventive strategies to individuals most at risk for bone loss are needed in order to reduce the incidence of fractures and the attendant costs to society. Alternatives to the available preventive drug therapies are needed in order to extend their utility to the largest possible number of people. Effective approaches to the treatment of established osteoporosis are urgently needed. Such new therapeutic approaches are most likely to arise from improved understanding of the basic biology of bone growth and maintenance.

Recent scientific and technological developments have markedly expanded opportunities for understanding the molecular and genetic basis of osteoporosis. Details are beginning to emerge of the complex network of signalling mechanisms that control bone growth and maintain skeletal integrity. Specific probes have made it possible to identify new molecules responsible for the local and systemic regulation of bone cell function, as well as the cell surface molecules and linked signal transduction pathways that mediate their effects. In particular, the complex relationship between the bone microenvironment and the immune system demands attention. The identification, mapping, and structural analysis of genes with crucial functions in the regulation of bone are increasingly feasible research goals. The use of genetically manipulated animals allows investigators to test the effects of specific gene inactivation or over-expression. The identification of genetic variations in the human population that underlie different vulnerabilities to bone loss is made possible by the increasing knowledge of the human genome and advancing molecular screening technology.

In order to capitalize on these opportunities, it is necessary to integrate biological insights and methodologies from a broad range of specialties. The overall goal of the Basic Osteoporosis New Experimental Strategies (BONES) initiative is to encourage and support new basic research in the areas of bone structure, formation, remodeling, and repair. This initiative is designed to (1) encourage established bone biology investigators to address osteoporosis-related problems with novel approaches and the most powerful methodologies available; (2) increase the pool of investigators working in osteoporosis-related basic science areas by drawing researchers from genetics, cell and molecular biology, and structural chemistry into bone research; and (3) foster the development of interactions between laboratories originating in different disciplines.

Research Goals and Scope

Some examples of research areas in which applications would be considered responsive to this RFA include, but are not limited to:

- o Mechanisms of action of growth factors, cytokines, bone inductive factors, and other regulators of bone growth and remodeling;
- o Genes and gene products with critical roles in bone growth and remodeling;
- o Mechanisms of action of estrogens, androgens, and glucocorticoids on bone;
- o Origins and lineages of osteoblasts, osteoclasts, and osteocytes: nature of precursor cells; control of activation, proliferation, and differentiation; role of marrow stromal stem cells;
- o Mechanisms of regulation of bone growth and remodeling by physical forces: loading stress, exercise, immobilization, and microgravity;
- o Biochemical and genetic markers of osteoporosis;
- o Biomechanical and non-invasive assessment of bone quality and architecture;
- o Influence of extracellular matrix composition and architecture on bone; growth and remodeling in normal and pathologic conditions;
- o Relationship between bone formation and vascularization in normal bone growth and fracture repair;

- o Cell and animal models for osteoporosis;
- o Effects of age and age-related changes on the level and action of hormones, growth factors, cytokines, and other osteotropic/osteogenic factors, and the impact and underlying mechanisms of such changes on bone remodeling and repair;
- o Elucidation of the nature and underlying mechanisms of age-related changes in the activation, proliferation and differentiation of bone cells and bone cell precursors; and
- o Determination of the mechanisms and consequences of age-related changes in bone vascularization and extracellular matrix on bone remodeling and bone architecture.

Investigators are not limited to the above examples of research areas, and are encouraged to propose other approaches that are appropriate to the R01 and R29 mechanisms and the requirements of this RFA.

STUDY POPULATIONS

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations), which have been in effect since 1990. The new policy contains some provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 9, 1994 (FR 59 11146-11151) and reprinted in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

(NOTE: When the proposed study or studies in the RFA or PA involves a gender specific study or a single or limited number of minority population groups, this should also be stated to inform potential applicants and reviewers.)

LETTER OF INTENT

Prospective applicants are asked to submit, by June 28, 1994, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows NIH staff to estimate the potential review workload and to avoid conflict of interest in the review.

The letter of intent is to be sent to Dr. William Sharrock at the address listed under INQUIRIES.

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 9/91) is to be used in applying for this RFA. These forms are available at most institutional offices of sponsored research; from the Office of Grants Information, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone 301-435-0714; and from the NIH program staff listed under INQUIRIES.

Applications for the FIRST Award (R29) must include at least three sealed letters of reference attached to the face page of the original application. FIRST Award (R29) applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

The RFA label available in the PHS 398 (rev. 9/91) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the

RFA title and number must be typed on line 2a of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and three signed photocopies, in one package to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

At the time of submission, two additional copies of the application must also be sent to:

Dr. Tommy Broadwater
Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 406
Bethesda, MD 20892
Telephone: (301) 594-9979
FAX: (301) 594-9673

Applications must be received by July 26, 1994. If an application is received after that date, it will be returned to the applicant without review. The Division of Research Grants (DRG) will not accept any application in response to this announcement that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The DRG will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the DRG and responsiveness by the NIAMS. Incomplete applications will be returned to the applicant without further consideration. If the application is not responsive to the RFA, NIAMS staff will contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next review cycle.

Applications may be triaged by an NIAMS peer review group on the basis of relative competitiveness. The NIH will withdraw from further competition those applications judged to be non-competitive for award and notify the applicant Principal Investigator and institutional official. Those applications judged to be competitive will undergo further scientific merit review. Those applications that are complete and responsive will be evaluated in accordance with the criteria stated below for scientific/technical merit by an appropriate peer review group convened by the NIAMS. The second level of review will be provided by the NIAMS, NIDDK, and NIA advisory councils.

Review criteria for RFAs are generally the same as those for unsolicited research grant applications.

- o extent to which the proposed research addresses the goals of the RFA;
- o scientific, technical, or medical significance and originality of proposed research;
- o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;
- o qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;
- o adequacy of plans for overall collaboration;
- o availability of the resources necessary to perform the research;
- o adequacy of the mechanisms for quality control, study monitoring, data management and reporting and data analysis;
- o adequacy of provisions for the protection of human subjects;
- o adequacy of the plans for inclusion of females and minorities; and
- o appropriateness of the proposed budget and duration in relation to the proposed research;

AWARD CRITERIA

The anticipated date of award is April 1, 1995. In addition to the technical merit of the application as reflected in the priority score, the NIAMS, NIDDK, and NIA will consider how well the applicant institution meets the goals and objectives of the program as described in the RFA, availability of resources and/or study populations.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged.

The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

William Sharrock, Ph.D.

Bone Biology and Bone Diseases Branch

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Westwood Building, Room 403

Bethesda, MD 20892

Telephone: (301) 594-9975

FAX: (301) 594-9673

Ronald Margolis, Ph.D.

Endocrinology Research Section

National Institute of Diabetes and Digestive and Kidney Diseases

Westwood Building, Room 621

Bethesda, MD 20892

Telephone: (301) 594-7549

FAX: (301) 594-9011

Sherry Sherman, Ph.D.

Geriatrics Program

National Institute on Aging

Gateway Building, Suite 2C218

7201 Wisconsin Avenue

Bethesda, MD 20892

Telephone: (301) 496-932

FAX: (301) 402-2945

Direct inquiries regarding fiscal matters to:

G. Carol Fitzpatrick
Grants Management Office
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 722A
Bethesda, MD 20892
Telephone: (301) 594-9974
FAX: (301) 594-9950

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.846, 93.847, and 93.866. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 410, 78th Congress, as amended, 42 USC 241 and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. The Public Health Service (PHS) strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the american people.

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